

SUPPLEMENTAL MATERIAL

Supplemental Methods

Frequency Matching

To select a day to start following patients who interrupted anticoagulation after the index major hemorrhage, we performed frequency matching. To do so, we simulated the distribution of the time to restart of anticoagulation for the groups that filled a prescription for an oral anticoagulation agent after the index major hemorrhage. The time to restart of drug in the dabigatran cohort followed a gamma distribution with $\alpha=1.17$ and $\sigma=47.5$. The time to restart of drug in the warfarin cohort followed a gamma distribution with $\alpha=1.12$ and $\sigma=54.2$. Start date after index major hemorrhage was set up so that the window between the date of the index major hemorrhage and start date followed a similar distribution to that of the time to anticoagulation restart among the subjects that restarted anticoagulation after the index major bleeding event.

Definition of Outcomes

A major bleeding event included any inpatient claims with primary or secondary ICD-9 codes for intracranial hemorrhage, hemoperitoneum, genitourinary hemorrhage, gastrointestinal hemorrhage, epistaxis, hemoptysis, vaginal hemorrhage, hemarthrosis, conjunctival hemorrhage or not otherwise specified hemorrhage (the list of ICD-9 codes is displayed in Table I).¹ Any bleeding event included any inpatient, emergency room or outpatient claim with primary or secondary ICD-9 codes for the same list of bleeding events. In order to avoid double counting, several claims for a bleeding event were considered the same single event if they occurred within 2 weeks of each other.²

Definition of Covariates

CHA2DS2-Vasc score measures of the risk of stroke in patients with AF. To calculate CHA2DS2-Vasc, female sex, age between 65 and 74, congestive heart failure, hypertension history, vascular disease history and diabetes mellitus are assigned one point, and age of 75 or older and a history of previous stroke, transient ischemic attack or thromboembolism are assigned two points.³

HAS-BLED score is a prediction score of the risk of major bleeding for patients with AF on anticoagulation. In calculating the HAS-BLED, age of 65 or greater, labile INR, renal disease, liver disease, use of antiplatelet agents or of nonsteroidal anti-inflammatory drugs (NSAIDs), and a history of hypertension, of stroke, of major bleeding and of alcohol or drug use are all assigned one point. Because claims data does not contain information on INR, we calculated the HAS-BLED score as the sum of all previous factors except labile INR.⁴

The number of other CMS priority comorbidities was calculated as the sum of previous a history of acquired hypothyroidism, Alzheimer's disease, related disorders or senile dementia, anemia, asthma, benign prostatic hyperplasia, cataract, chronic obstructive pulmonary disease, ischemic heart disease, hip or pelvic fracture, glaucoma, hyperlipidemia, osteoporosis, rheumatoid arthritis or osteoarthritis, breast cancer, colorectal cancer, prostate cancer, lung cancer and endometrial cancer.

Vascular disease was defined as having at least one outpatient claim with primary or secondary ICD-9 codes 440.0x, 440.2x, 440.9x, 441.3x, 441.4x, 441.5x, 441.9x, 443.9x, 444.22, 444.81, 447.1x, 443.81, 250.70, 433.10, 433.11, 433.30 in the year before index major hemorrhage.⁵

Liver disease was defined as having at least one outpatient claim with primary or secondary ICD-9 code 571.xx in the year before index major hemorrhage.⁶

Alcohol or drug usage history was defined as having at least one outpatient claim with primary or secondary ICD-9 codes 303.xx, 304.xx, 305.xx in the year before index major hemorrhage.

Use of NSAIDS was defined as filling a prescription for diclofenac, ibuprofen, naproxen, ketoprofen, fenoprofen, flurbiprofen, piroxicam, meloxicam, mefenamic acid or indomethacin in the six months before the date of the first major hemorrhage; and use of antiplatelet drugs was defined as filling a prescription for aspirin, clopidogrel, prasugrel, dipyridamole, ticlopidine or ticagrelor in the six months before the date of the index major hemorrhage.¹

Receiving a transfusion was defined as having at least one procedure with ICD-9 procedure code 990.xx during the inpatient stay for the index bleeding event.

To identify which patients underwent a corrective surgical procedure, we extracted all ICD-9 procedure codes recorded during the inpatient stay for the index major hemorrhage, and selected the procedures whose objective was to correct the anatomical area where the bleeding event had happened (the list of qualifying ICD-9 procedure codes for corrective surgical procedures in each anatomical area can be found in Table I at <http://stroke.ahajournals.org>).

To identify a history of chronic kidney disease, hypertension, stroke or transient ischemic attack, acute myocardial infarction, diabetes, and congestive heart failure, we used the CMS Chronic Condition Warehouse (CCW) indicators that trace back the diagnosis of these conditions to January 1, 1999.⁷

Supplemental Table I. International Classification of Diseases, Ninth Revision (ICD-9) Codes for Bleeding Events and for Corrective Surgical Procedures by Anatomical Site.

Bleeding Event	ICD-9 Diagnosis Codes to Identify Bleeding Events	ICD-9 Procedure Codes to Identify Corrective Procedures
Intracranial bleeding	430, 431, 432	N/A
Hemoperitoneum	568.81	54.12, 54.4
Hematuria	599.7	57.49, 57.93
GI Hemorrhage	530.7, 531.0, 531.2, 531.4, 531.6, 532.0, 532.2, 532.4, 532.6, 533.0, 533.2, 533.4, 533.6, 534.0, 534.2, 534.4, 534.6, 569.3, 535.01, 535.11, 535.21, 535.31, 535.41, 535.51, 535.61, 535.71, 537.83, 537.84, 562.02, 562.03, 562.12, 562.13, 569.85, 578	42.33, 43.41, 43.89, 44.29, 44.42, 44.43, 44.44, 45.30, 45.34, 45.42, 45.43, 45.73, 45.74, 45.76, 45.82, 45.93, 46.20, 48.35, 48.36
Epistaxis	784.7	21.01, 21.02, 21.03, 21.05, 21.31, 21.61
Hemoptysis	786.3	30.29, 31.1, 31.69, 32.20
Vaginal Hemorrhage	623.8, 626.2	N/A
Hemarthrosis	719.1, 719.2	81.92
Conjunctival hemorrhage	372.72	12.4
NOS Hemorrhage	459	Any of the listed codes

Notes:

Abbreviations: GI=Gastrointestinal; NOS=Not Otherwise Specified.

Supplemental Table II. Time to Post-Hemorrhage Anticoagulation Resumption, Follow-up Period, and Patterns of Post-Hemorrhage Anticoagulation Use, by Treatment Group and Study Cohort.

	Resumed Dabigatran (n=117)	No Oral Anticoagulant Use (n=217)	Switched to Warfarin (n=70)	P-Value
Dabigatran Cohort- Mean (SD)				
Time from first major bleeding to anticoagulant re-start (days)	45 (49)	--	73 (84)	0.005
Follow-up period after first major bleeding (days)	396 (167)	335 (201)	432 (166)	<0.001
Patterns of post-hemorrhage anticoagulant use (%)				
Switched anticoagulant treatment	18.0	--	1.4	<0.001
Discontinued anticoagulant therapy	3.4	--	47.1	<0.001
Warfarin Cohort- Mean (SD)				
Time from first major bleeding to anticoagulant re-start (days)	Resumed Warfarin (n=484)	No Oral Anticoagulant Use (n=626)	Switched to Dabigatran (n=25)	P-Value
Full cohort	60 (72)	--	70 (60)	0.501
Patients with intracranial index bleeding	109 (77)	--	64 (64)	0.353
Follow-up period after first major bleeding (days)	371 (205)	333 (205)	457 (211)	<0.001
Patterns of post-hemorrhage anticoagulant use (%)				
Switched anticoagulant treatment	3.1	--	8.0	0.184
Discontinued anticoagulant therapy	6.4	--	28.0	<0.001

Supplemental Table III. Number of Events and Unadjusted Cumulative Incidence Rates of Post-Hemorrhage Clinical Outcomes, by Cohort and Post-Hemorrhage Treatment Group.

Dabigatran Cohort	Resumed Dabigatran (n=117)	No Oral Anticoagulation (n=217)	Switched to Warfarin (n=70)
Effectiveness Outcomes			
Ischemic Stroke and All-Cause Mortality			
Number of events (%)	21 (18.0)	48 (22.1)	13 (18.6)
Cumulative incidence (95% CI)			
At 3 months	0.07 (0.02 , 0.12)	0.18 (0.13 , 0.24)	0.13 (0.05 , 0.21)
At 6 months	0.13 (0.07 , 0.19)	0.21 (0.15 , 0.27)	0.15 (0.06 , 0.23)
At 1 yr	0.21 (0.13 , 0.29)	0.26 (0.19 , 0.33)	0.22 (0.11 , 0.33)
Ischemic Stroke			
Number of events (%)	20 (17.1)	23 (10.6)	12 (17.1)
Cumulative incidence (95% CI)			
At 3 months	0.06 (0.02 , 0.11)	0.07 (0.03 , 0.11)	0.12 (0.04 , 0.20)
At 6 months	0.12 (0.06 , 0.18)	0.08 (0.04 , 0.13)	0.13 (0.05 , 0.22)
At 1 yr	0.20 (0.12 , 0.29)	0.15 (0.08 , 0.21)	0.21 (0.10 , 0.32)
All-Cause Mortality			
Number of events (%)	2 (1.7)	25 (11.5)	2 (2.9)
Cumulative incidence (95% CI)			
At 3 months	0.01 (0.00 , 0.03)	0.12 (0.07 , 0.16)	0.03 (0.00 , 0.07)
At 6 months	0.02 (0.00 , 0.04)	0.13 (0.08 , 0.18)	0.03 (0.00 , 0.07)
At 1 yr	0.02 (0.00 , 0.04)	0.13 (0.08 , 0.18)	0.03 (0.00 , 0.07)
Safety Outcomes			
Major Recurrent Hemorrhage			
Number of events (%)	8 (6.8)	13 (6.0)	6 (8.6)
Cumulative incidence (95% CI)			
At 3 months	0.04 (0.00 , 0.07)	0.05 (0.02 , 0.08)	0.06 (0.00 , 0.11)
At 6 months	0.06 (0.01 , 0.10)	0.05 (0.02 , 0.09)	0.06 (0.00 , 0.11)
At 1 yr	0.07 (0.02 , 0.11)	0.09 (0.04 , 0.14)	0.09 (0.01 , 0.17)
Any Recurrent Hemorrhage			
Number of events (%)	40 (34.2)	60 (27.7)	26 (37.1)
Cumulative incidence (95% CI)			
At 3 months	0.24 (0.16 , 0.32)	0.24 (0.18 , 0.30)	0.26 (0.16 , 0.36)
At 6 months	0.29 (0.21 , 0.37)	0.31 (0.24 , 0.38)	0.29 (0.18 , 0.40)
At 1 yr	0.34 (0.25 , 0.44)	0.40 (0.31 , 0.49)	0.38 (0.25 , 0.51)

Warfarin Cohort	Resumed Warfarin (n=484)	No Oral Anticoagulation (n=626)	Switched to Dabigatran (n=25)
Effectiveness Outcomes			
Ischemic Stroke and All-Cause Mortality			
Number of events (%)	92 (19.0)	144 (23.0)	6 (24.0)
Cumulative incidence (95% CI)			
At 3 months	0.10 (0.07 , 0.13)	0.20 (0.17 , 0.23)	0.18 (0.02 , 0.33)
At 6 months	0.16 (0.12 , 0.19)	0.23 (0.20 , 0.27)	0.23 (0.05 , 0.40)
At 1 yr	0.23 (0.18 , 0.27)	0.26 (0.23 , 0.30)	0.28 (0.09 , 0.48)
Ischemic Stroke			
Number of events (%)	66 (13.6)	67 (10.7)	5 (20.0)
Cumulative incidence (95% CI)			
At 3 months	0.06 (0.04 , 0.09)	0.09 (0.06 , 0.11)	0.14 (0.00 , 0.28)
At 6 months	0.11 (0.07 , 0.14)	0.11 (0.08 , 0.14)	0.19 (0.02 , 0.36)
At 1 yr	0.17 (0.13 , 0.21)	0.14 (0.11 , 0.18)	0.25 (0.06 , 0.44)
All-Cause Mortality			
Number of events (%)	27 (5.6)	86 (13.7)	1 (4.0)
Cumulative incidence (95% CI)			
At 3 months	0.03 (0.02 , 0.05)	0.14 (0.11 , 0.17)	0.04 (0.00 , 0.13)
At 6 months	0.06 (0.03 , 0.08)	0.15 (0.12 , 0.18)	0.04 (0.00 , 0.13)
At 1 yr	0.07 (0.04 , 0.09)	0.15 (0.12 , 0.18)	0.04 (0.00 , 0.13)
Safety Outcomes			
Major Recurrent Hemorrhage			
Number of events (%)	68 (14.1)	44 (7.0)	1 (4.0)
Cumulative incidence (95% CI)			
At 3 months	0.08 (0.06 , 0.11)	0.06 (0.04 , 0.08)	0.00 (0.00 , 0.00)
At 6 months	0.11 (0.08 , 0.14)	0.08 (0.06 , 0.11)	0.00 (0.00 , 0.00)
At 1 yr	0.17 (0.13 , 0.21)	0.10 (0.07 , 0.13)	0.00 (0.00 , 0.00)
Any Recurrent Hemorrhage			
Number of events (%)	170 (35.1)	188 (30.0)	5 (20.0)
Cumulative incidence (95% CI)			
At 3 months	0.26 (0.22 , 0.30)	0.29 (0.25 , 0.33)	0.17 (0.02 , 0.33)
At 6 months	0.33 (0.29 , 0.38)	0.35 (0.30 , 0.39)	0.17 (0.02 , 0.33)
At 1 yr	0.42 (0.37 , 0.47)	0.39 (0.34 , 0.43)	0.17 (0.02 , 0.33)

NOTES:

Cumulative incidence of clinical events was calculated from Kaplan-Meier time-to-event curves.

Supplemental Table IV. Anatomical Location of the Recurrent Bleeding Event, by Anatomical Location of the First Major Hemorrhage and Treatment Group.

Location of Any Recurrent Bleeding Event										
Dabigatran Cohort					Warfarin Cohort					
Resumed Dabigatran					Resumed Warfarin					
	IC	GI	Hematuria	Other	No Bleeding	IC	GI	Hematuria	Other	No Bleeding
IC (n=0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	IC (n=20)	5 (25.0)	0 (0.0)	0 (0.0)	2 (10.0) 13 (65.0)
GI (n=92)	1 (1.1)	22 (23.9)	3 (3.3)	3 (3.3)	63 (68.5)	GI (n=337)	4 (1.2)	85 (25.2)	5 (1.5)	21 (6.2) 222 (65.9)
Hematuria (n=5)	0 (0.0)	1 (20.0)	2 (40.0)	0 (0.0)	2 (40.0)	Hematuria (n=42)	1 (2.4)	0 (0.0)	11 (26.2)	4 (9.5) 26 (61.9)
Other (n=20)	0 (0.0)	2 (10.0)	1 (5.0)	5 (25.0)	12 (60.0)	Other (n=85)	2 (2.4)	10 (11.8)	3 (3.5)	17 (20.0) 53 (62.4)
Switched to Warfarin					Switched to Dabigatran					
IC (n=5)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	5 (100.0)	IC (n=3)	0 (0.0)	0 (0.0)	0 (0.0)	3 (100.0)
GI (n=53)	1 (1.1)	16 (30.2)	2 (3.8)	3 (5.7)	31 (58.5)	GI (n=19)	0 (0.0)	3 (15.8)	1 (5.3)	14 (74.7)
Hematuria (n=2)	1 (50.0)	0 (0.0)	0 (0.0)	1 (50.0)	0 (0.0)	Hematuria (n=1)	0 (0.0)	0 (0.0)	0 (0.0)	1 (100.0)
Other (n=10)	0 (0.0)	1 (10.0)	0 (0.0)	1 (10.0)	8 (80.0)	Other (n=2)	0 (0.0)	0 (0.0)	0 (0.0)	2 (100.0)
No Post-Hemorrhage Oral Anticoagulation Use					No Post-Hemorrhage Oral Anticoagulation Use					
IC (n=23)	5 (21.7)	1 (4.35)	1 (4.35)	1 (4.35)	15 (65.2)	IC (n=116)	26 (22.4)	2 (1.7)	3 (2.6)	3 (2.6) 82 (70.7)
GI (n=184)	1 (0.5)	38 (20.7)	5 (2.7)	6 (3.3)	134 (72.8)	GI (n=426)	3 (0.7)	107 (25.1)	8 (1.9)	12 (2.8) 296 (69.5)
Hematuria (n=5)	0 (0.0)	0 (0.0)	1 (20.0)	0 (0.0)	4 (80.0)	Hematuria (n=18)	1 (5.6)	0 (0.0)	4 (22.2)	0 (0.0) 13 (72.2)
Other (n=5)	0 (0.0)	0 (0.0)	0 (0.0)	1 (20.0)	4 (80.0)	Other (n=66)	0 (0.0)	4 (6.1)	2 (3.0)	13 (19.7) 47 (71.2)

NOTES:

Abbreviations: IC=Intracranial; GI=Gastrointestinal.

Supplemental Table V. Results of Sensitivity Analyses.

Dabigatran cohort	Adjusted Hazard Ratio (% CI)						
	Resumed Dabigatran vs No Oral Anticoagulant Use		Switched to Warfarin vs No Oral Anticoagulant Use		Switched to Warfarin vs Resumed Dabigatran		
	Sensitivity Analysis	Base Case	Sensitivity Analysis	Base Case	Sensitivity Analysis	Base Case	
Effectiveness Outcomes							
Ischemic Stroke/All-Cause Mortality	0.64 (0.38-1.10)	0.67 (0.40-1.15)	0.57 (0.28-1.14)	0.70 (0.38-1.31)	0.88 (0.42-1.88)	1.04 (0.52-2.09)	
All-Cause Mortality	0.13 (0.03-0.56)	0.13 (0.03-0.58)	0.11 (0.01-0.82)	0.21 (0.05-0.91)	0.83 (0.08-9.20)	1.57 (0.22-11.18)	
Ischemic Stroke	1.24 (0.65-2.34)	1.29 (0.69-2.43)	1.17 (0.54-2.54)	1.29 (0.63-2.65)	0.95 (0.44-2.03)	1.00 (0.48-2.09)	
Safety Outcomes							
Major Recurrent Hemorrhage	0.71 (0.28-1.83)	0.68 (0.27-1.72)	1.20 (0.44-3.30)	1.08 (0.41-2.88)	1.69 (0.57-5.00)	1.47 (0.58-3.72)	
Any Recurrent Hemorrhage	0.91 (0.60-1.39)	0.87 (0.58-1.32)	1.23 (0.76-1.98)	1.04 (0.65-1.66)	1.34 (0.81-2.24)	1.20 (0.70-2.00)	
Warfarin cohort	Resumed Warfarin vs No Oral Anticoagulant Use		Switched to Dabigatran vs No Oral Anticoagulant Use		Switched to Dabigatran vs Resumed Warfarin		
	Sensitivity Analysis	Base Case	Sensitivity Analysis	Base Case	Sensitivity Analysis	Base Case	
Effectiveness Outcomes							
Ischemic Stroke/All-Cause Mortality	0.71 (0.54-0.95)	0.75 (0.57-0.98)	0.72 (0.26-1.95)	0.96 (0.42-2.19)	1.00 (0.37-2.74)	1.28 (0.56-2.94)	
All-Cause Mortality	0.35 (0.22-0.55)	0.35 (0.23-0.55)	0.29 (0.04-2.12)	0.27 (0.04-1.95)	0.84 (0.11-6.23)	0.77 (0.11-5.69)	
Ischemic Stroke	1.25 (0.84-1.86)	1.26 (0.88-1.80)	1.31 (0.41-4.26)	1.81 (0.72-4.53)	1.05 (0.33-3.37)	1.43 (0.57-3.58)	
Safety Outcomes							
Major Recurrent Hemorrhage	1.63 (1.09-2.44)	1.60 (1.09-2.36)	0.42 (0.06-3.06)	0.38 (0.05-2.79)	0.26 (0.04-1.85)	0.24 (0.03-1.73)	
Any Recurrent Hemorrhage	0.94 (0.75-1.18)	0.95 (0.77-1.18)	0.50 (0.20-1.21)	0.42 (0.17-1.02)	0.53 (0.22-1.28)	0.44 (0.18-1.08)	

Supplemental Table V continued

Two cohorts combined	Dabigatran vs No Oral Anticoagulant Use				Dabigatran vs Warfarin	
	Warfarin vs No Oral Anticoagulant Use				Sensitivity Analysis	Base Case
Effectiveness Outcomes	Sensitivity Analysis	Base Case	Sensitivity Analysis	Base Case	Sensitivity Analysis	Base Case
Ischemic Stroke/All-Cause Mortality	0.71 (0.55-0.92)	0.76 (0.59-0.97)	0.60 (0.39-0.93)	0.66 (0.44-0.99)	0.85 (0.55-1.33)	0.87 (0.57-1.33)
All-Cause Mortality	0.33 (0.22-0.51)	0.35 (0.23-0.53)	0.13 (0.04-0.41)	0.13 (0.04-0.41)	0.39 (0.12-1.29)	0.37 (0.11-1.22)
Ischemic Stroke	1.24 (0.76-2.02)	1.27 (0.93-1.75)	1.24 (0.88-1.76)	1.37 (0.86-2.17)	1.00 (0.62-1.61)	1.07 (0.68-1.69)
Safety Outcomes						
Major Recurrent Hemorrhage	1.61 (1.12-2.32)	1.56 (1.10-2.22)	0.68 (0.33-1.39)	0.65 (0.32-1.33)	0.42 (0.21-0.85)	0.42 (0.21-0.84)
Any Recurrent Hemorrhage	0.99 (0.81-1.21)	0.97 (0.80-1.17)	0.80 (0.58-1.11)	0.77 (0.56-1.07)	0.80 (0.58-1.12)	0.80 (0.58-1.10)

Notes:

Bold denotes statistical significant results.

Results from sensitivity analyses represent adjusted hazard ratios of post-hemorrhage clinical outcomes calculated before and after excluding patients who experienced an intracranial bleeding event.

Supplemental References

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